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FAVISM

PAGET DAVIES, M.B., M.R.C.P.
*Senior Medical Registrar, King's College Hospital, London, S.E.5**

FAVISM is characterized by acute hæmolysis occurring in sensitive subjects after inhalation of the pollen or ingestion of the seed of the broad bean plant. Recently it has been shown that the sensitivity is due to a deficiency of glucose-6-phosphate dehydrogenase in the erythrocytes of the sufferer (Sansone, Piga, and Segni, 1958).

Such an abnormality links favism with primaquine-induced hæmolytic anæmia and explains the pathogenesis of a disease long hidden in obscurity (Alving, Kellermeyer, Tarlov, Schrier, and Carson, 1958).

Favism has been thought to be a disease of great antiquity and the dictum 'Pythagorei faba se abstinuerunt' has been held to imply that Pythagoras was aware of the disorder. This was disputed by Solon Veras in 1939 (cited by Sansone, Piga, and Segni, 1958) for he could find no account of the disease by ancient writers who might have been expected to have described favism, if it occurred, with their customary attention to detail. He concluded that the Veto of Pythagoras was an instruction to avoid indulgence, since Pythagoras prohibited his followers not only from eating beans but also certain meats and fishes. Iamblichus, too, has suggested that many sacred and physical causes accounted for the Veto. However, Arie (1959) concluded that Pythagoras suffered from favism for, rather than enter a field of broad beans, he was slain by the pursuing people of Croton (Diogenes Laertius). His followers, when pursued by Dionysius, died almost to a man on the edge of a field of broad beans. Of the two survivors, Myllas preferred to die and his wife Timycha bit out her tongue rather than divulge the reason for not entering the field (Iamblichus).

Sansone, Piga, and Segni (1958) attributed the first reference to favism to Mira Franco who, in 1843, described the disease in Portugal. Six years earlier, however, Mörike (1837) had written about favism minor which is caused by inhalation of the pollen of the broad bean plant.

Vicia faba minor
Fort mit diesem Geruch, dem zauberhaften: Er mahnt mich
An die Haare, die mir einst alle Sinne bestrickt.
Weg mit dieser Blüte, der schwarzen und weissen! Sie sagt mir,
Dass die Verführerin, ach! schwer mit dem Tode gebusst!

Many observations, especially by Italian workers, have appeared in the latter half of the 19th century A.D. More recently Luisada (1941) has reviewed the problem of favism and Sansone, Piga, and Segni (1958) have summarized their experience in book form.

Favism occurs principally in the Mediterranean lands, especially Sardinia. In 1956, Crosby noted that among a population of 1¼ millions on the island, the incidence of favism was five per 1,000, the highest in the world. The death rate had been as high as 250 in 1936. He postulated that the spread of favism was due to the Phœnicians, Romans, Greeks and Carthaginians having taken the Sardinians as slaves, but this does not account for the disease appearing in the Jews of Oriental origin (non-Ashkenazis) or the negroes of the North American continent. Luisada (1941) has suggested that its appearance in America could be due to the influx of Mediterranean races and that broad beans are a staple article of diet.

Apart from Sardinia, favism occurs in numerous localities of Southern Italy and there is no doubt the disease is widespread, the cases reported being only a small proportion of those occurring. After Sardinia and Italy, the next most important centre is Iraq. Here the isolated Jewish community has intermarried for 2,500 years. It is descended from the Judeans carried into captivity by Nebuchadnezzar in 588 B.C. (Jeremiah lii, 28), who preferred to remain in Babylon where they were prospering rather than return to Palestine under Zerubbabel in 536 B.C. by decree of Cyrus (Ezra ii, 1).

Parallel with the spread of the peoples of Mediterranean origin has been the cultivation of the broad bean plant throughout the world. Originating in Persia near to the Caspian Sea

* Present address: Brighton General Hospital, Brighton 7

and possibly in North Africa, it owes its ubiquity to its ability to grow on and enrich an impoverished soil. Despite this, the plant had been in danger of extinction since its seed had no means of dispersal. Its struggle for existence would have ended had man not saved it by cultivation. The plant was known a thousand years before Christ (2 Samuel xvii, 28), introduced into Europe by the Celts and Slavs, and taken to China a century before the Christian era (de Candolle, 1884).

During the past eight years the condition has been recognized in Britain (Diggle, 1953; Discombe and Mestitz, 1956; Gower and Frommer, 1960). Nearly all the victims have been of Italian, Greek or Jewish ancestry and Discombe and Mestitz (1956) have pointed out 'the present Völkerwanderungen are bringing to our shores examples of disease which once had to be sought half a world away'. However, favism has been recognized in an English-born child (McCarthy, 1955) and more recently in two English-born women. One was seen by the author in 1958 and the second was reported in a preliminary communication by Brodribb and Worssam (1961).

Etiology

Our knowledge of favism today is due to Crosby (1956). He suggested applying in subjects with a history of favism, the tests developed by Alving and his colleagues in the investigation of primaquine-induced hæmolytic anæmia (Alving, Kellermeyer, Tarlov, Schrier, and Carson, 1958). Their work and that of other investigators has shown that both primaquine- and fava-induced hæmolytic anæmia are associated with a deficiency of glucose-6-phosphate dehydrogenase activity in the erythrocyte so that glutathione is not reduced effectively (Fig. 1).

FIG. 1.—Glutathione metabolism in the erythrocyte.

$$\text{G-6-P} + \text{TPN}^+ \overset{\text{G-6-PD}}{\rightleftarrows} \text{6-PG} + \text{TPNH}^+ + \text{H}^+$$

$$\text{GSSG} + \text{TPNH} + \text{H}^+ \overset{\text{GR}}{\rightarrow} 2\text{GSH} + \text{TPN}^+$$

Key:

G-6-P and G-6-PD	= glucose-6-phosphate and its dehydrogenase.
TPN^+ and TPNH	= Oxidized and reduced triphosphopyridine nucleotide.
H^+	= hydrogen ions.
GSSG and GSH	= oxidized and reduced glutathione.
GR	= glutathione reductase.

Both the stability of glutathione and the activity of erythrocyte glucose-6-phosphate dehydrogenase have been used to investigate the inheritance of the biochemical defect. Childs, Zinkham, Browne, Kimbro and Torbert (1958) concluded that transmission was by a sex-linked incompletely-dominant gene although a sex-limited autosomal gene could not be excluded. The author has had the opportunity to study the inheritance of this defect in the family of the boy reported by McCarthy (1955) and the family of the English woman who had the disease in 1958. The enzyme defect was found to be transmitted by a sex-linked dominant gene with variable expression in the female (to be published).

Clinical Features

During a visit to Cagliari to observe favism, 21 patients admitted under the care of Professor Fiaschi were seen. No children were present in the series, which was collected in a unit for adults. It contained approximately equal numbers of males and females (11 : 10). The sex incidence was comparable to that recorded in adults by Sansone, Piga and Segni (1958), who noted, however, that the disease had a predilection for the first decade of life: approximately nine-tenths of those children affected are males. In 17 patients, hæmolysis had followed the eating of broad beans; six had eaten fresh beans and six cooked beans; the remaining five had eaten both fresh and cooked beans. Hæmolysis may occur after eating only a few beans as in one of the patients seen, and Luisada (1941) has recorded favism in a child of 5 years who ate a single bean!

Only four patients in the present series had developed favism after inhalation of the pollen from the blossom of the broad bean plant. Of 1,211 patients with favism reported by Fermi (1905), 62% of the attacks followed ingestion of the bean (favism major) and 38% inhalation of the pollen (favism minor). The latter type of attack occurs during a walk in or near the fields where the plants are in bloom. Since the pollen is sticky and small in amount, favism minor is obviously rare in towns.

Only one patient had never eaten broad beans before, forewarned perhaps by favism occurring in both her father and paternal uncle. Unfortunately, in her case, hæmolysis had been caused by inhalation of the pollen. Eight patients had eaten beans previously without suffering an attack. Nevertheless, the remaining 12 had had previous episodes of hæmolysis after eating beans, some more than once, and in one coma had resulted.

A family history of favism was obtained in eight patients; the brother of one had died at the age of 2 years as a result of an attack.

The onset of favism was marked by malaise, nausea, and vomiting associated with headache, vertigo and even pain in the lumbar region. In one patient symptoms appeared within minutes

of inhaling the pollen. After ingestion of the beans, symptoms were delayed up to 24 hours. Later, from 24 to 48 hours, the specific symptoms due to hæmolysis appeared: jaundice and hæmoglobinuria. These two features were those which caused the patients to consult their doctor. The severity of the hæmolytic anæmia was the factor necessitating the patient's admission to hospital. Since the anæmia was accompanied by jaundice, the skin has been described as pale-green in colour and this was regarded as a diagnostic feature of favism (Fiaschi, 1960). With the hæmolysis an irregular fever reaching as much as 101° F. (38.4° C.) appeared. As a result of anæmia the patient complained of dyspnœa and palpitation, a tachycardia of up to 130 per minute being observed, although the blood pressure was unaffected. Hepatomegaly was not seen and splenomegaly noted in but four patients, two of whom had had malaria.

During the attack, anæmia was invariable and was sometimes severe: values for the hæmoglobin ranged from 3 g. per 100 ml. to 12 g. per 100 ml. in one patient who was seen 12 days after the onset. A reticulocytosis occurred and with it a moderate leucocytosis affecting the neutrophils. In all 21 patients albuminuria was found and occasionally casts were seen in the urine. Hæmoglobinuria was not always found as it disappeared after the third day. Luisada (1941) has observed that if it persisted then usually the patient died. Of more importance was the oliguria which occurred in five patients and was associated with a rise in the blood urea. Lioia (1947) recorded in one patient that at necropsy the kidneys showed normal glomeruli but degenerative changes in the tubules. These, he likened to those described in the renal anoxia syndrome by Maegraith, Havard and Parsons (1945). More recently Casper and Shulman (1956) have recorded bilateral cortical renal necrosis in a Jewish breast-fed male infant who died at the age of 6 months. Five days prior to his death, his mother had eaten broad beans. Although she remained well, the infant developed jaundice and hæmoglobinuria due presumably to favism. The possibility that the hæmolytic factor of the bean can be transmitted via the milk was supported by the patient recorded by Luisada (1941) in which favism followed the drinking of milk from a goat which had eaten broad beans.

Once the acute episode was over, recovery was the rule. In one patient favism in the past had been complicated by coma and in the present by pneumonia. The mortality rate has been quoted at about 8% (Fermi, 1905) and may be due to renal failure. One patient had a blood urea of 117 mg. per 100 ml. but recovered. The sibling of another patient had died of favism. The disease causes much disability, partly due to the poverty and consequent malnutrition of the Sardinians. As a result, the patients were often anæmic prior to hæmolysis and required transfusion of blood and multiple hæmatinics. Nevertheless, as a consequence of early transfusion the mortality in children has fallen from between 20 and 40% to 5% (Crosby, 1956). In Sardinia, however, subjects with a past history of favism are precluded from being donors.

One patient is of particular interest. Favism occurred only in later life and followed inhalation of the pollen. In addition, he developed allergic symptoms such as wheezing, malaise and rhinitis. His daughter developed hæmolysis after treatment with quinine for malaria. Freedman, Barr and Brody (1956) recorded hæmolysis after quinidine, while more recently Gilles and Ikeme (1960) have reported hæmoglobinuria due to drug sensitivity in Nigerians with deficiency of erythrocyte glucose-6-phosphate dehydrogenase activity.

If an attack is survived, temporary immunity may result. Presumably this is due to the destruction of the senescent erythrocytes low in glucose-6-phosphate dehydrogenase activity, leaving the younger and more resistant cells with much enzyme activity. Antihistamines and corticosteroids have been used (Becker, 1954), but seemed of no value. Obviously prevention consists of avoiding exposure to the pollen and the seed of the broad bean plant. In Sardinia this is of some importance and difficulty. There are many large fields of beans since it is an easy crop to grow on a poor soil, and in fact enhances the nitrogen content of the soil. Beans are eaten fresh as a fruit at all meals except breakfast. The Sardinians have a curious indifference to favism. Although aware that the beans are the cause of the complaint, they continue to eat the fruit. Of course, favism does not follow after every occasion when beans have been eaten.

Favism is seasonal in its occurrence, being seen from April to May in Sardinia, and April to July in Great Britain, when the broad bean plant is in blossom and fruit. Nevertheless, as in the patient recorded by Gower and Frommer (1960) it can occur at any time of the year, since beans can be preserved in a deep-freeze refrigerator.

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